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EFFECT OF DIET AND PNEUMOCOCCAL INFECTION ON PROTEIN  
DYNAMICS OF BLOOD LY. (U) ARMY MEDICAL RESEARCH INST OF  
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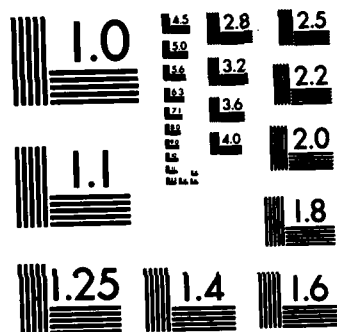
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Effect of diet and pneumococcal infection on protein dynamics of  
blood lymphocytes in cynomolgus monkeys

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In conducting the research described in this report, the  
investigators adhered to the "Guide for the Care and Use of  
Laboratory Animals," as promulgated by the Committee on Care  
and Use of Laboratory Animals of the Institute of Laboratory  
Animal Resources, National Research Council. The facilities  
are fully accredited by the American Association for Accreditation  
of Laboratory Animal Care.

The views of the authors do not purport to reflect the positions of  
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) → Blood lymphocytes play an important role in host defense against infectious disease. To determine the effect of diet and infection on lymphocyte protein dynamics, cynomolgus monkeys received daily i.v. infusion of either 8% dextrose (34 kcal/kg), 4.25% amino acids (16 kcal/kg) or AA + D solutions. On day 2, 6 cynomolgus monkeys in each group received either live (infected, I) or heat-killed (control) <i>S. pneumoniae</i> . All cynomolgus monkeys were given a constant infusion of [ <sup>14</sup> C]leucine. By 6 h, the specific activity (SA) of the leucine		

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→ in the protein-free filtrate of plasma had reached a plateau. A blood sample was then removed and the SA was determined on isolated leucine. I increased the rate of turnover and breakdown of total body protein. 8% dextrose significantly reduced leucine turnover and release in the breakdown of total body protein compared to 4.5% amino acids or amino acids + dextrose. When infused with amino acids, the rate of protein synthesis of leucine was significantly increased compared to dextrose alone. Mitogen stimulation and protein content were significantly greater in the leucine from cynomolgus monkeys infused with amino acids compared to dextrose. Amino acids + dextrose had values between amino acids and dextrose. Presence of I reduced the stimulation index, but had no effect on protein content or fractional protein synthetic rate. Thus, while dextrose infusion decreased turnover of body protein, it was less effective than amino acids in promoting functional activity and protein synthesis of leucine. ↑

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## Introduction

In a recent workshop in "Nutritional support of the patient: research direction for the 80's", it was stressed that there is a need for nutrient support in patients with life-threatening infections and who had lost 10% of their body weight (Wilmore and Kinney, 1981). These experts also stressed importance of development of support therapy that would optimally stimulate host defense against infectious disease. It was also recommended that research on nutritional support and infection requires investigations in both animals and man. An important factor in developing a rational approach to nutritional supportive therapy in infected individuals is the knowledge of the effects of the various nutrients on protein dynamics in various cells and tissues of the body. It has been previously demonstrated that adequate calories and amino acids will prevent protein wasting during sepsis in the monkey, (Wannemacher et al., 1978). This conclusion is based on nitrogen balance data, which represent the algebraic sum of the protein dynamics in various tissue compartments. Nutrient support therapy can improve the immune response in a protein-calorie depleted patient. There is, however, very little data on the comparative effects of amino acid and dextrose calories on stimulating immune response or protein dynamics of leukocytes in either infected or noninfected monkeys.

## Experimental Procedure

Thirty-six male cynomolgus monkeys were divided into 3 groups of 12 each. All monkeys had catheters implanted in the jugular and femoral veins and were maintained in metabolic cages via a jacketed-tethering system. On day 3 after surgery the monkeys were infused via the jugular vein with either 8% dextrose (34 cal/kg), 4.25% amino acids (16 cal/kg), or dextrose plus amino acid (50 cal/kg/day). In addition, each solution contained similar amounts of vitamins, electrolytes and trace elements. One day after starting on the nutrient support solutions 6 monkeys in each group received in i.v. dose of  $2 \times 10^8$  live S. pneumoniae or  $2 \times 10^8$  heat-killed S. pneumoniae. The monkeys receiving the heat-killed organisms served as noninfected controls. Two days after

receiving the microorganisms [ $^{14}\text{C}$ ]leucine was infused over a 6-hour time period. By 6 hours after  $^{14}\text{C}$  infusion the specific activity of the leucine in the protein-free filtrate of plasma had reached a plateau which is indicative of a constant precursor pool. At this 6-hour time period a blood sample was removed and specific activity of leucine was measured in samples of mixed leukocyte proteins. Lymphocytes were separated by sedimentation of the red cells in dextran, followed by centrifugation in lymphocyte separating media. Specific activity was measured in the mixed proteins of this cellular pool. Another sample of blood was removed at 6-hour time period and utilized to measure mitogen stimulation of lymphocyte blastogenesis by concanavalin A (Con A), phytohemagglutinin (PHA), or pokeweed mitogen (PWM).

## Results

Infusion of 8% dextrose solution significantly reduced leucine turnover and release from breakdown of total body protein as compared to infusion of 4.25% amino acids (Table I). Amino acid plus dextrose infusion tended to be intermediate between the other 2 groups. In all 3 groups, presence of infection increased the rate of leucine turnover and breakdown of total body protein. Nitrogen balance was poorest in the dextrose group and best in the amino acid plus dextrose monkeys. Infectious disease decreased nitrogen imbalance in all 3 groups; however, dextrose plus amino acid group was still in positive balance.

No differences were observed between dextrose or amino acid infusion on blood lymphocyte concentrations but pneumococcal sepsis did result in a decrease in blood lymphocyte counts. The stimulation index for lymphocytes by all 3 mitogens was significantly greater in the monkeys receiving i.v. amino acids as compared to those infused with dextrose (Table I). In all 3 groups pneumococcal sepsis markedly reduced the stimulation produced by various mitogens.

The protein content of lymphocytes from control monkeys infused with amino acids was significantly greater than those infused with dextrose or dextrose plus amino acids. Infection tended to reduce total lymphocyte protein content in all 3 groups.

The fractional rate of synthesis of mixed lymphocyte proteins was significantly lower in monkeys infused with dextrose as compared to amino acids (Table I). The amino acid plus dextrose group tended to fall intermediate between the 2 other groups.

### Conclusions

1. Intravenous infusion of amino acids and/or dextrose has marked effects on breakdown of total body protein and synthesis of mixed lymphocyte proteins.
2. While dextrose infusion tended to conserve body protein by decreasing the rate of turnover of total body protein, it markedly inhibited the immune response and fractional rate of synthesis of mixed lymphocyte proteins.
3. Infusion of amino acids resulted in a greater turnover of body protein but resulted in a marked increase in lymphocyte blastogenesis and mixed protein synthesis as compared to dextrose infusions. The amino acid plus dextrose infusions tended to fall intermediate between the other nutrient support therapies.
4. Infectious disease increased leucine release and protein breakdown in all 3 nutrient support therapies. Only the addition of amino acids plus dextrose prevented severe wasting of body protein. Pneumococcal sepsis tended to reduce mitogen stimulation in lymphocytes but had no effect on its fractional rate of protein synthesis.
5. These observations raised the question as to whether measurements of only protein loss can be used as a criteria for assessing the value of a nutrient support therapy in stimulating host defense against infectious disease.

### References

1. Wannemacher, R. W., Jr., Kaminski, M. V., Jr., Neufeld, H. A., Dinterman, R. E., Bostian, K. A., and Hadick, C. L. (1978): Protein-sparing therapy during pneumococcal infection in rhesus monkeys. JPEN, 2:507-518.
2. Wilmore, D. W. and Kinney, J. M. (1981): Panel report on nutritional support of patients with trauma or infection. J. Am. Clin. Nutr., 34:1213-1222.

Table I. Effect of intravenous amino acids and/or glucose on total body protein dynamics, mitogen stimulation of lymphocyte blastogenesis, and mixed lymphocyte protein dynamics.

Treatment	Leucine Turnover $\mu\text{moles/kg}\cdot\text{hr}^{-1}$	Stimulation Index <sup>a</sup>			Fractional synthetic rate of lymphocyte protein %/day
		Con A	PHA	PWM	
4.25% Amino acids <sup>b</sup>					
Control	438 $\pm$ 37 <sup>c</sup>	10.69 $\pm$ 1.19	40.52 $\pm$ 7.16	24.43 $\pm$ 2.51	33.1 $\pm$ 5.1
Infected	614 $\pm$ 96 <sup>d</sup>	4.29 $\pm$ 1.13 <sup>c</sup>	5.09 $\pm$ 2.05 <sup>c</sup>	4.80 $\pm$ 1.17 <sup>d</sup>	42.1 $\pm$ 8.4
8% Dextrose					
Control	62 $\pm$ 11	5.38 $\pm$ 1.30	15.16 $\pm$ 2.23	12.66 $\pm$ 3.37	2.76 $\pm$ 1.17
Infected	90 $\pm$ 9	2.05 $\pm$ 0.52	3.49 $\pm$ 1.05 <sup>c</sup>	2.9 $\pm$ 0.85 <sup>d</sup>	2.08 $\pm$ 0.74
4.25% Amino acid + 8% dextrose					
Control	348 $\pm$ 14	5.06 $\pm$ 0.92	15.39 $\pm$ 1.81	30.74 $\pm$ 8.70	19.2 $\pm$ 4.1
Infected	406 $\pm$ 18	1.95 $\pm$ 0.30	5.62 $\pm$ 1.01	4.28 $\pm$ 0.98	16.5 $\pm$ 3.9

<sup>a</sup> Stimulation index = DPM in mitogen stimulated lymphocytes / DPM in non-stimulated lymphocytes

<sup>a</sup> Stimulation index =  $\frac{\text{DPM in mitogen stimulated lymphocytes}}{\text{DPM in non-stimulated lymphocytes}}$

<sup>b</sup> Leucine intake 243  $\mu\text{moles/kg}\cdot\text{hr}^{-1}$

<sup>c</sup> Mean  $\pm$  SE of six monkeys

<sup>d</sup> P < 0.01 compared to control